(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076386 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/07967

(22) International Filing Date: 18 March 2002 (18.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/278,891 26 March 2001 (26.03.2001) US

(71) Applicants *(for all designated States except US)*: **ZYMOGENETICS, INC.** [US/US]; 1201 Eastlake Avenue East, Seattle, WA 98102 (US). **UNIVERSITY OF WASHINGTON** [US/US]; Seattle, WA 98195 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MOORE, Emma, E.** [US/US]; 3507 30th Avenue West, Seattle, WA 98199 (US). **REH, Thomas** [US/US]; 9006 25th Avenue NE, Seattle, WA 98115 (US).

(74) Agent: **LUNN, Paul, G.**; Zymo Genetics, Inc., 1201 Eastlake Avenue East, Seattle, WA 98102 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076386 A2

(54) Title: METHOD OF INDUCING PROLIFERATION OF RETINAL STEM CELLS

(57) Abstract: The present invention relates to a method for promoting the proliferation of retinal stem cells using IL-17B. IL-17B is put into a cell culture medium containing retinal stem cells to promote the proliferation and/or differentiation of retinal stem cells. The retinal stem cells can then be transplanted into the retina to promote the growth of the photoreceptor cells, the rods and the cones. Also IL-17B can be administered directly into the retina to promote the proliferation and/or differentiation of the retinal stem cells.

METHOD OF INDUCING PROLIFERATION OF RETINAL STEM CELLS

BACKGROUND OF THE INVENTION

Vision is one of the most important special senses in humans. Light enters the eye and impinges on photoreceptors of a specialized epithelium, the retina. The photoreceptors include rods and cones. Rods have low thresholds for detecting light and operate best under conditions of reduced lighting (scoptic vision). However, rods neither provide well-defined visual images nor contribute to color vision. Cones, by contrast, are not as sensitive as rods to light and so operate best under daylight conditions (photopic vision). Cones are responsible for high visual acuity and color vision.

Information processing within the retina is performed by retinal interneurons, and the output signals are carried to the brain by the axons of retinal ganglion cells. Fetal and adult retinal stem cells give rise to all the various cell types in the retina including a) the rod and the cone photoreceptors, b) the horizontal, bipolar, and amacrine interneurons, c) the ganglion projection neurons, and d) the Muller glia cells.

Degenerative diseases of the retina often result in blindness due to the destruction of the rods or cones. Retinal stem cell therapy has been developed in which retinal stem cells are harvested from the patient grown and expanded in culture and reintroduced into the retina in an attempt to promote regeneration of the rods and cones. Growth factors that have been used in culture to promote proliferation of the retinal stem cells include a) transforming growth factor alpha (TGF-α) and epidermal growth factor (EGF), b) fibroblast growth factor (FGF), c) TGF-β 2 & 3, and d) sonic hedgehog (shh). While these growth factors are useful, there is still a need to discover additional agents to promote the proliferation and differentiation of retinal stem cells into photoreceptor rods or cones.

DESCRIPTION OF THE INVENTION

The present invention fills this need by providing for a method of promoting the proliferation of retinal stem cells comprising bringing IL-17B into contact with retinal stem cells. Retinal stem cells can be grown in culture into which IL-17B is added and re-implanted into a patient's retina to produce functioning rods and cones of the retina. Alternatively, the IL-17B can be administered directly into retina.

The teachings of all of the references cited in the present specification are incorporated in their entirety herein by reference.

Definitions

The term "effective amount" as used herein regarding the effective amount of IL-17B administered in accordance with the present invention means an amount of IL-17B that causes proliferation of retinal stem cells. The effective amount of IL-17B or IL-17 to be administered is from 0.1 μg to 100 μg of IL-17B or IL-17 per kilogram of body weight per day. More preferably, the effective amount is from 1 μg to 500 μg of IL-17B or IL-17 per kilogram of body weight. IL-17B should be administered daily until the symptoms of neuropathy dissipate. If the retinal stem cells are grown in culture, the concentration of IL-17B in the culture medium should be at least 100 ng/ml.

IL-17B (formerly called 'Zcyto7') and a method for making IL-17B polypeptides have been disclosed in International Patent Application No. PCT/US98/08212, Publication No. WO 98/49310.

Introduction

The present invention is based upon the discovery that IL-17B or IL-17 can induce the proliferation and/or differentiation of retinal stem cells. IL-17B can be used to treat many ocular disorders in which retinal neurons have degenerated, such as macular degeneration and glaucoma. Age-related macular degeneration is the leading cause of blindness in the United States. Currently, there is no satisfactory treatment. In promoting the proliferation of retinal stem cells, one can administer IL-17B directly into the retina or by a gene therapy modality to stimulate the growth of endogenous stem cells. Secondly, retinal stem cells can be removed from the patient and IL-17B can

be used to stimulate the growth of retinal stem cells *in vitro,* and then transplant the stem cells back into the retina of the patient.

Those skilled in the art will recognize that the sequences disclosed in SEQ ID NOs: 1, and 2 represent a single allele of the human IL-17B. One can clone allelic variants of these sequences by probing cDNA or genomic libraries from different individuals according to standard procedures.

Modes of Administration

In general, pharmaceutical formulations will include an IL-17B protein in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington: *The Science and Practice of Pharmacy,* Gennaro, ed., (Mack Publishing Co., Easton, PA, 19th ed., 1995). In a culture medium in which retinal stem cells are growing, the IL-17B should be present at a concentration of at least 100 ng/ml. If the IL-17B is administered directly into the retina, the therapeutic doses will generally be in the range of 0.1 to 100 μg/kg of patient weight, with the exact dose determined by the clinician according to accepted standards determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years.

Nucleic Acid-based Therapeutic Treatment

IL-17B can be also administered to a retinal stem cell by means of gene therapy. In one embodiment, a gene encoding an IL-17B polypeptide is introduced *in vivo* in a viral vector. Such vectors include an attenuated or defective DNA virus, such as but not limited to herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adeno-associated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes virus 1 (HSV1) vector [Kaplitt *et al., Molec. Cell. Neurosci.2*: 320-330 (1991)], an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet *et al., J. Clin. Invest. 90* :626-630 (1992), and a defective adeno-associated

virus vector [Samulski *et al., J. Virol., 61*:3096-3101 (1987); Samulski *et al. J. Virol., 63*:3822-3828 (1989)].

In another embodiment, the gene can be introduced into a retinal stem cell by means of a retroviral vector, *e.g.*, as described in Anderson *et al.*, U.S. Patent No. 5,399,346; Mann *et al., Cell, 33*:153 (1983); Temin *et al.*, U.S. Patent No. 4,650,764; Temin *et al.*, U.S. Patent No. 4,980,289; Markowitz *et al., J. Virol. 62*:1120 (1988); Temin *et al.*, U.S. Patent No. 5,124,263; International Patent Publication No. WO 95/07358, published March 16, 1995 by Dougherty *et al.* and *Blood, 82*:845 (1993).

Alternatively, the vector can be introduced by lipofection *in vivo* using liposomes. Synthetic cationic lipids can be used to prepare liposomes for *in vivo* transfection of a gene encoding a marker [Felgner *et al., Proc. Natl. Acad. Sci. USA, 84*:7413-7417 (1987); see Mackey *et al., Proc. Natl. Acad. Sci. USA, 85*:8027-8031 (1988)]. The use of lipofection to introduce exogenous genes into specific organs *in vivo* has certain practical advantages. Molecular targeting of liposomes to specific cells represents one area of benefit. It is clear that directing transfection to particular cells represents one area of benefit. It is clear that directing transfection to particular cell types would be particularly advantageous in a tissue with cellular heterogeneity, such as the pancreas, liver, kidney, and brain. Lipids may be chemically coupled to other molecules for the purpose of targeting. Targeted peptides, *e.g.*, hormones or neurotransmitters, and proteins such as antibodies, or non-peptide molecules could be coupled to liposomes chemically.

It is possible to remove the retinal stem cells from the body and introduce the vector as a naked DNA plasmid and then re-implant the transformed cells into the body. Naked DNA vector for gene therapy can be introduced into the desired host cells by methods known in the art, *e.g.*, transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun or use of a DNA vector transporter [see, *e.g.*, Wu *et al., J. Biol. Chem., 267*:963-967 (1992); Wu *et al., J. Biol. Chem., 263*:14621-14624 (1988)].

Example 1
Cloning of IL-17B

IL-17B was identified from expressed sequence tag (EST) 582069 (SEQ ID NO: 3) by its homology to Interleukin-17. The EST582069 cDNA clone was obtained from the IMAGE™ consortium Lawrence Livermore National Laboratory through Genome Systems, Inc. The cDNA was supplied as an agar stab containing *E. coli* transfected with the plasmid having the cDNA of interest and then streaked out on an LB 100 µg/ml ampicillin and 100 µg/ml methicillin plate. The cDNA insert in EST582069 was sequenced. The insert was determined to be 717 base pairs long with a 180 amino acid open reading frame and a 22 amino acid signal peptide.

Example 2
Construction of IL-17B Expression Vectors

A 473 bp IL-17B PCR DNA fragment was generated with 1 µl of a dilution of the EST582069 plasmid prep of Example 2 and 20 picomoles (pm) of primer SEQ ID NO: 4 and 20 pm primer SEQ ID NO: 5. The digested reaction mixture was electrophoresed on a 1% TBE gel; the DNA band was excised with a razor blade and the DNA was extracted from the gel with the Qiaquick« Gel Extraction Kit (Qiagen). The excised DNA was subcloned into plasmid nfpzp9, which had been cut with *Bam* and *Xho*. Nfpzp9 is a mammalian cell expression vector comprising an expression cassette containing the mouse metallothionein-1 promoter, a sequence encoding the tissue plasminogen activator (TPA) leader, then multiple restriction sites. These were followed by the human growth hormone terminator, an *E. coli* origin of replication and a mammalian selectable marker expression unit containing the SV40 promoter, enhancer and origin of replication, a dihydrofolate reductase gene (DHFR) and the SV40 terminator.

IL-17B was purified by means of affinity chromatography using anti-IL-17B antibodies.

Example 3
Cloning of Murine IL-17B

Mouse IL-17B was identified from an expressed sequence tag (EST) 660242 (SEQ ID NO: 8). EST660242 cDNA clone was obtained from the IMAGE consortium Lawrence Livermore National Laboratory through Genome Systems, Inc. The cDNA was supplied as an agar stab containing E. coli transfected with the plasmid having the cDNA of interest and then streaked out on an LB 100 μg/ml ampicillin, 25 μg/ml methicillin plate. The cDNA insert in EST660242 was sequenced. The insert was determined to be 785 base pairs with an open reading frame of 180 amino acids and a putative 20 amino acid signal peptide. The sequences are defined by SEQ ID NO: 7 and SEQ ID NO: 6.

Example 4
Proliferation of Retinal Stem Cells in Culture

Retinal stem cells were obtained from the retina of E17-18 rat embryos and grown in culture. Preliminary results indicate that human recombinant IL-17B stimulates the growth of retinal stem cells. The cells spread out on the substrate within one day, and the IL-17B-treated cells appeared to proliferate more rapidly than the control cells. We verified that IL-17B stimulated the proliferation of these cells by using an antibody that recognizes a protein present in M-phase cells (phosphohistone3). We found many more cells labeled with phospho-histone3 antibody in the culture containing the IL-17B.

CLAIMS

We claim:

1. A method for inducing the proliferation and/or differentiation of retinal stem cells comprising bringing the retinal stem cells into contact with interleukin-17B (IL-17B).

2. The method of claim 1 wherein the IL-17B polypeptide is selected from the group consisting of SEQ ID NOs: 2, 7, and 9-28.

3. The method of claim 1 wherein the retinal stem cells are grown in a culture medium.

4. The method of claim 3 wherein the retinal stem cells are implanted into the retina of a mammal after the stems cells have come into contact with IL-17B.

5. A method for inducing the proliferation and/or differentiation of retinal stem cells comprising administering IL-17B into the retina.

SEQUENCE LISTING

<110> ZymoGenetics, Inc.
University of Washington
Emma E. Moore
Thomas Reh

<120> Method for Proliferation of Retinal Stem Cells

<130> 01-13PC

<150> 60/278,891
<151> 2001-03-26

<160> 28

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 736
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (57)...(596)

<400> 1

```
gaattcggca cgaggaggcg ggcagcagct gcaggctgac cttgcagctt ggcgga atg      59
                                                                 Met
                                                                  1

gac tgg cct cac aac ctg ctg ttt ctt ctt acc att tcc atc ttc ctg      107
Asp Trp Pro His Asn Leu Leu Phe Leu Leu Thr Ile Ser Ile Phe Leu
             5                  10                  15

ggg ctg ggc cag ccc agg agc ccc aaa agc aag agg aag ggg caa ggg      155
Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly
         20                  25                  30

cgg cct ggg ccc ctg gcc cct ggc cct cac cag gtg cca ctg gac ctg      203
Arg Pro Gly Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu
     35                  40                  45

gtg tca cgg atg aaa ccg tat gcc cgc atg gag gag tat gag agg aac      251
Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn
 50                  55                  60                  65

atc gag gag atg gtg gcc cag ctg agg aac agc tca gag ctg gcc cag      299
Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln
                 70                  75                  80

aga aag tgt gag gtc aac ttg cag ctg tgg atg tcc aac aag agg agc      347
Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser
             85                  90                  95

ctg tct ccc tgg ggc tac agc atc aac cac gac ccc agc cgt atc ccc      395
Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro
         100                 105                 110
```

```
gtg gac ctg ccg gag gca cgg tgc ctg tgt ctg ggc tgt gtg aac ccc      443
Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro
    115                 120                 125

ttc acc atg cag gag gac cgc agc atg gtg agc gtg ccg gtg ttc agc      491
Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser
130                 135                 140                 145

cag gtt cct gtg cgc cgc cgc ctc tgc ccg cca ccg ccc cgc aca ggg      539
Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly
                150                 155                 160

cct tgc cgc cag cgc gca gtc atg gag acc atc gct gtg ggc tgc acc      587
Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr
            165                 170                 175

tgc atc ttc tgaatcacct ggcccagaag ccaggccagc agcccgagac             636
Cys Ile Phe
        180

catcctcctt gcacctttgt gccaagaaag gcctatgaaa agtaaacact gacttttgaa    696
agccagaaaa aaaaaaaaaa aaaaaaattc ctgcggccgc                          736
```

<210> 2
<211> 180
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Asp Trp Pro His Asn Leu Leu Phe Leu Leu Thr Ile Ser Ile Phe
 1               5                  10                  15
Leu Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln
            20                  25                  30
Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp
        35                  40                  45
Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
    50                  55                  60
Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala
65                  70                  75                  80
Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg
                85                  90                  95
Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
            100                 105                 110
Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
        115                 120                 125
Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
    130                 135                 140
Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr
145                 150                 155                 160
Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys
                165                 170                 175
Thr Cys Ile Phe
            180
```

<210> 3
<211> 397
<212> DNA
<213> Homo sapiens

<400> 3

```
aggcgggcan agctgcaggc tgaccttgca gcttggcgga atggactggc ctcacaacct     60
gctgtttctt cttaccattt ccatcttcct ggggctgggc agccaggagc cccaaaagca    120
```

agaggaaggg gcaagggcgg cctgggcccn tggcctggcc tcaccaggtg ccactggacc 180
tggtgtcacg gatgaaaccg tatgcccgca tggaggagta tgagaggaac atcgaggaga 240
tggtggccca gctgaggaac agctcanaag ctggcccaga gaaagtgtga ggtcaacttg 300
cagctgtgga tgtccaacaa gaaggagcct gtctcccttg gggctacaag catcaaccac 360
cgaccccagc cgtatccccg tgggaccttg ccgggac 397

<210> 4
<211> 18
<212> DNA
<213> Homo sapiens

<400> 4
ttaccatttc catcttcc 18

<210> 5
<211> 18
<212> DNA
<213> Homo sapiens

<400> 5
cccttcctct tgcttttg 18

<210> 6
<211> 692
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (50)...(589)

<400> 6
ggggttcctg gcgggtggca gctgcgggcc tgccgcctga cttggtggg atg gac tgg 58
Met Asp Trp
1

ccg cac agc ctg ctc ttc ctc ctg gcc atc tcc atc ttc ctg gcg cca 106
Pro His Ser Leu Leu Phe Leu Leu Ala Ile Ser Ile Phe Leu Ala Pro
5 10 15

agc cac ccc cgg aac acc aaa ggc aaa aga aaa ggg caa ggg agg ccc 154
Ser His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln Gly Arg Pro
20 25 30 35

agt ccc ttg gcc cct ggg cct cat cag gtg ccg ctg gac ctg gtg tct 202
Ser Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser
40 45 50

cga gta aag ccc tac gct cga atg gaa gag tat gag cgg aac ctt ggg 250
Arg Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Leu Gly
55 60 65

gag atg gtg gcc cag ctg agg aac agc tcc gag cca gcc aag aag aaa 298
Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala Lys Lys Lys
70 75 80

tgt gaa gtc aat cta cag ctg tgg ttg tcc aac aag agg agc ctg tcc 346
Cys Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg Ser Leu Ser
85 90 95

cca tgg ggc tac agc atc aac cac gac ccc agc cgc atc cct gcg gac 394
Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Ala Asp

```
100                 105                 110                 115

ttg ccc gag gcg cgg tgc cta tgt ttg ggt tgc gtg aat ccc ttc acc      442
Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr
                120                 125                 130

atg cag gag gac cgt agc atg gtg agc gtg cca gtg ttc agc cag gtg      490
Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val
            135                 140                 145

ccg gtg cgc cgc cgc ctc tgt cct caa cct cct cgc cct ggg ccc tgc      538
Pro Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro Gly Pro Cys
        150                 155                 160

cgc cag cgt gtc gtc atg gag acc atc gct gtg ggt tgc acc tgc atc      586
Arg Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile
    165                 170                 175

ttc tgagccaacc accaacccgg tggcctctgc aacaaccctc cctccctgca          639
cccactgtga ccctcaaggc tgataaacag taaacgctgt tctttgtaaa gga          692
```

<210> 7
<211> 179
<212> PRT
<213> Mus musculus

<400> 7

```
Met Asp Trp Pro His Ser Leu Leu Phe Leu Leu Ala Ile Ser Ile Phe
 1               5                  10                  15
Leu Ala Pro Ser His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln
            20                  25                  30
Gly Arg Pro Ser Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp
        35                  40                  45
Leu Val Ser Arg Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
    50                  55                  60
Asn Leu Gly Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala
65                  70                  75                  80
Lys Lys Lys Cys Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg
                85                  90                  95
Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
            100                 105                 110
Pro Ala Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
        115                 120                 125
Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
    130                 135                 140
Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro
145                 150                 155                 160
Gly Pro Cys Arg Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys
                165                 170                 175
Thr Cys Ile
```

<210> 8
<211> 497
<212> DNA
<213> Mus musculus

<400> 8

```
ggggttcctg gcgggtggca gctgcgggcc tgccgcctga cttggtggga tggactggcc      60
gcacagcctg ctcttcctcc tggccatctc catcttcctg gcgccaagcc acccccggaa     120
caccaaaggc aaaagaaaag ggcaagggag gcccagtccc ttggcccctg ggctcatcag     180
gtgccgctgg acctggtgtc tcgagtaaag ccctacgctc gaatggaaga gtatgagcgg     240
```

aaccttgggg agatggtggc ccagctgagg aacagctccg agccagccaa gaagaaatgt 300
gaagtcaatc tacagctgtg gttgtccaac aagaggagcc tgtccccatg gggctacagc 360
atcaaccacg accccagccg catccctgcg gacttgcccg aggcgcggtg cctatgtttg 420
ggttgcgtga atcccttcac catgcaggag gaccgtagca tggtgagcgt gccagtgttc 480
agccaggtgc cggtgcg 497

<210> 9
<211> 160
<212> PRT
<213> Homo sapiens

<400> 9

Gln	Pro	Arg	Ser	Pro	Lys	Ser	Lys	Arg	Lys	Gly	Gln	Gly	Arg	Pro	Gly
1				5					10					15	
Pro	Leu	Ala	Pro	Gly	Pro	His	Gln	Val	Pro	Leu	Asp	Leu	Val	Ser	Arg
			20					25					30		
Met	Lys	Pro	Tyr	Ala	Arg	Met	Glu	Glu	Tyr	Glu	Arg	Asn	Ile	Glu	Glu
		35					40					45			
Met	Val	Ala	Gln	Leu	Arg	Asn	Ser	Ser	Glu	Leu	Ala	Gln	Arg	Lys	Cys
	50					55					60				
Glu	Val	Asn	Leu	Gln	Leu	Trp	Met	Ser	Asn	Lys	Arg	Ser	Leu	Ser	Pro
65					70					75					80
Trp	Gly	Tyr	Ser	Ile	Asn	His	Asp	Pro	Ser	Arg	Ile	Pro	Val	Asp	Leu
				85					90					95	
Pro	Glu	Ala	Arg	Cys	Leu	Cys	Leu	Gly	Cys	Val	Asn	Pro	Phe	Thr	Met
			100					105					110		
Gln	Glu	Asp	Arg	Ser	Met	Val	Ser	Val	Pro	Val	Phe	Ser	Gln	Val	Pro
		115					120					125			
Val	Arg	Arg	Arg	Leu	Cys	Pro	Pro	Pro	Pro	Arg	Thr	Gly	Pro	Cys	Arg
	130					135					140				
Gln	Arg	Ala	Val	Met	Glu	Thr	Ile	Ala	Val	Gly	Cys	Thr	Cys	Ile	Phe
145					150					155					160

<210> 10
<211> 160
<212> PRT
<213> Homo sapiens

<400> 10

Gln	Pro	Arg	Ala	Pro	Lys	Ser	Lys	Arg	Lys	Gly	Gln	Gly	Arg	Pro	Gly
1				5					10					15	
Pro	Leu	Ala	Pro	Gly	Pro	His	Gln	Val	Pro	Leu	Asp	Leu	Val	Ser	Arg
			20					25					30		
Met	Lys	Pro	Tyr	Ala	Arg	Met	Glu	Glu	Tyr	Glu	Arg	Asn	Ile	Glu	Glu
		35					40					45			
Met	Val	Ala	Gln	Leu	Arg	Asn	Ser	Ser	Glu	Leu	Ala	Gln	Arg	Lys	Cys
	50					55					60				
Glu	Val	Asn	Leu	Gln	Leu	Trp	Met	Ser	Asn	Lys	Arg	Ser	Leu	Ser	Pro
65					70					75					80
Trp	Gly	Tyr	Ser	Ile	Asn	His	Asp	Pro	Ser	Arg	Ile	Pro	Val	Asp	Leu
				85					90					95	
Pro	Glu	Ala	Arg	Cys	Leu	Cys	Leu	Gly	Cys	Val	Asn	Pro	Phe	Thr	Met
			100					105					110		
Gln	Glu	Asp	Arg	Ser	Met	Val	Ser	Val	Pro	Val	Phe	Ser	Gln	Val	Pro
		115					120					125			
Val	Arg	Arg	Arg	Leu	Cys	Pro	Pro	Pro	Pro	Arg	Thr	Gly	Pro	Cys	Arg
	130					135					140				
Gln	Arg	Ala	Val	Met	Glu	Thr	Ile	Ala	Val	Gly	Cys	Thr	Cys	Ile	Phe
145					150					155					160

<210> 11
<211> 160

<212> PRT
<213> Homo sapiens

<400> 11
Gln Pro Arg Ser Pro Lys Ala Lys Arg Lys Gly Gln Gly Arg Pro Gly
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20 25 30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
35 40 45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50 55 60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65 70 75 80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85 90 95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100 105 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115 120 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
130 135 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145 150 155 160

<210> 12
<211> 160
<212> PRT
<213> Homo sapiens

<400> 12
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Ala
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20 25 30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
35 40 45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50 55 60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65 70 75 80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85 90 95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100 105 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115 120 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
130 135 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145 150 155 160

<210> 13
<211> 160
<212> PRT
<213> Homo sapiens

<400> 13
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ala Arg
20 25 30

```
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160

      <210> 14
      <211> 160
      <212> PRT
      <213> Homo sapiens

      <400> 14
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
 1               5                  10                  15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
            20                  25                  30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160

      <210> 15
      <211> 160
      <212> PRT
      <213> Homo sapiens

      <400> 15
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
 1               5                  10                  15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
            20                  25                  30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
```

```
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Leu Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160
```

<210> 16
<211> 160
<212> PRT
<213> Homo sapiens

<400> 16

```
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
 1               5                  10                  15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
            20                  25                  30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Phe Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160
```

<210> 17
<211> 160
<212> PRT
<213> Homo sapiens

<400> 17

```
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
 1               5                  10                  15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Gly Arg
            20                  25                  30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160
```

<210> 18
<211> 160
<212> PRT
<213> Homo sapiens

<400> 18
Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Ser
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20 25 30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
35 40 45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50 55 60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65 70 75 80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85 90 95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100 105 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115 120 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
130 135 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145 150 155 160

<210> 19
<211> 160
<212> PRT
<213> Homo sapiens

<400> 19
Gln Pro Arg Ser Pro Lys Val Lys Arg Lys Gly Gln Gly Arg Pro Gly
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20 25 30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
35 40 45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50 55 60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65 70 75 80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85 90 95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100 105 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115 120 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
130 135 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145 150 155 160

<210> 20
<211> 160
<212> PRT
<213> Homo sapiens

<400> 20
Gln Pro Arg Val Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly

```
 1               5                  10                  15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
            20                  25                  30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
        35                  40                  45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
    50                  55                  60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65                  70                  75                  80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
                85                  90                  95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
            100                 105                 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
        115                 120                 125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
    130                 135                 140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160
```

<210> 21
<211> 158
<212> PRT
<213> Homo sapiens

<400> 21

```
Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu
 1               5                  10                  15
Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys
            20                  25                  30
Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val
        35                  40                  45
Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val
    50                  55                  60
Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly
65                  70                  75                  80
Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu
                85                  90                  95
Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu
            100                 105                 110
Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg
        115                 120                 125
Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg
    130                 135                 140
Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155
```

<210> 22
<211> 154
<212> PRT
<213> Homo sapiens

<400> 22

```
Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro
 1               5                  10                  15
His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg
            20                  25                  30
Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg
        35                  40                  45
Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu
    50                  55                  60
Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn
```

65 70 75 80
His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu
85 90 95
Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met
100 105 110
Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys
115 120 125
Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu
130 135 140
Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145 150

<210> 23
<211> 151
<212> PRT
<213> Homo sapiens

<400> 23
Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His Gln Val
1 5 10 15
Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu
20 25 30
Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser
35 40 45
Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser
50 55 60
Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro
65 70 75 80
Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly
85 90 95
Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val
100 105 110
Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro
115 120 125
Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala
130 135 140
Val Gly Cys Thr Cys Ile Phe
145 150

<210> 24
<211> 160
<212> PRT
<213> Homo sapiens

<400> 24
His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln Gly Arg Pro Ser
1 5 10 15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20 25 30
Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Leu Gly Glu
35 40 45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala Lys Lys Lys Cys
50 55 60
Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg Ser Leu Ser Pro
65 70 75 80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Ala Asp Leu
85 90 95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100 105 110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115 120 125
Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro Gly Pro Cys Arg

```
    130                 135                 140
Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155                 160
```

<210> 25
<211> 158
<212> PRT
<213> Homo sapiens

<400> 25

```
Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln Gly Arg Pro Ser Pro Leu
 1               5                  10                  15
Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Val Lys
            20                  25                  30
Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Leu Gly Glu Met Val
        35                  40                  45
Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala Lys Lys Lys Cys Glu Val
    50                  55                  60
Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly
65                  70                  75                  80
Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Ala Asp Leu Pro Glu
                85                  90                  95
Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu
            100                 105                 110
Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg
        115                 120                 125
Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro Gly Pro Cys Arg Gln Arg
    130                 135                 140
Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150                 155
```

<210> 26
<211> 153
<212> PRT
<213> Homo sapiens

<400> 26

```
Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His
 1               5                  10                  15
Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met
            20                  25                  30
Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn
        35                  40                  45
Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp
    50                  55                  60
Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His
65                  70                  75                  80
Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys
                85                  90                  95
Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val
            100                 105                 110
Ser Val Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro
        115                 120                 125
Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr
    130                 135                 140
Ile Ala Val Gly Cys Thr Cys Ile Phe
145                 150
```

<210> 27
<211> 128
<212> PRT
<213> Homo sapiens

<400> 27
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
1 5 10 15
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
20 25 30
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
35 40 45
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
50 55 60
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
65 70 75 80
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
85 90 95
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
100 105 110
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
115 120 125

<210> 28
<211> 157
<212> PRT
<213> Homo sapiens

<400> 28
Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu
1 5 10 15
Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys
20 25 30
Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val
35 40 45
Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val
50 55 60
Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly
65 70 75 80
Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu
85 90 95
Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu
100 105 110
Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg
115 120 125
Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg
130 135 140
Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile
145 150 155